Ann Med Res 2021;28(3):527-31

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.05.466

Original Article

The role of monocyte to lymphocyt ratio in predicting metastasis in rectal cancer

Oguz Catal[1], Bahri Ozer[1], Mustafa Sit[1], Gulali Aktas[2], Hayri Erkol[1]

[1]Department of General Surgery, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey

Abstract

Aim: A lot of studies are being carried out to predict recurrence and metastasis in rectal cancer, which is a common type of cancer in general surgery practice. It is thought that MLR (monocyte to lymphocyte ratio) , an indice developed by division of monocyte count by lymphocyte count, may be a good marker to reflect the degree of tumor progression and predict prognosis. In our study, we investigated the role of MLR in predicting metastasis in rectal cancer.

Materials and Methods: Fifty-seven patients diagnosed with rectal cancer in the Abant Izzet Baysal University general surgery clinic between 2012 and 2016 were retrospectively investigated. Albumin, CRP(C reactive protein), Platelet, Neutrophil, Lymphocyte, Monocyte values were obtained as the inflammatory markers in the blood count test of the patients before neoadjuvant treatment.

Results: In this study, 25 patients who underwent neoadjuvant chemoradiotherapy and underwent full postoperative follow-up were evaluated. Eight of these 25 patients had metastasis until June 2019. There was a significant difference in monocyte and MLR values between groups with and without metastasis.

Conclusion: This study is presented as a preliminary study. In our study, we showed that MLR value which measured before neoadjuvant therapy in rectum cancer patients may be useful in predicting metastasis development.

Keywords: Metastasis; monocyte; monocyte to lymphocyte ratio; rectum cancer

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth leading cause of cancer-related death. Rectal cancer accounts for approximately 30-50% of colorectal cancers (1). A lot of studies are being carried out to predict metastasis in rectal cancer, which is a common type of cancer general surgery practice.

There is growing interest in tumor cells, molecular pathways, mutation states, inflammation and immune cell infiltration in predicting the prognosis of CRC. Systemic inflammatory response has been reported to play a critical role in the pathogenesis and progression of cancer, including CRC (2). Tumor-associated leukocytes, particularly monocytes, the main regulators of cancer-related inflammation, have been shown to play an important role in the systemic inflammatory response to tumor cells (3).

Macrophages, which originate from monocytes, develop from mononuclear phagocytic progeny cells with specific phenotypic properties. The role of macrophages / monocytes in the development and progression of cancer is controversial, since there are studies that showed monocytes can increase or inhibit the development of cancer (4). It is thought that MLR, an indice developed by division of monocyte count by lymphocyte count, may be a good marker to reflect the degree of tumor progression and predict prognosis (5).

Monocyte and lymphocyte counts and monocyte to lymphocyte ratio (MLR) obtained from blood count test were proposed to be associated with survival and prognosis in various types of cancer(6).

In this study, we investigated the role of MLR which is one of the inflammatory markers in routine hemogram test before neoadjuvant chemoradiotherapy in patients undergoing neadjuvant chemoradiotherapy as a preliminary study to determine the risks of metastasis in patients with rectal cancer.

MATERIALS and METHODS

Patients diagnosed with colorectal cancer between 2012 and 2016 in BAIBU Medical Faculty General Surgery clinic were evaluated retrospectively. All of the patients

Received: 11.05.2020 **Accepted:** 06.08.2020 **Available online:** 19.03.2021
Corresponding Author: Oguz Catal, Department of General Surgery, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey **E-mail:** otuzogur@gmail.com

received neoadjuvant chemoradiotherapy (CRT) and were waited for 4-6 weeks after the completion of neoadjuvant therapy. Only patients who completed at least 3 years of follow up after diagnosed with rectal cancer and treated with neoadjuvant chemoradiotherapy were included to the study. Patients who received neoadjuvant CRT, who could not be operated due to concomitant diseases, who did not receive neoadjuvant CRT, who did not receive adjuvant therapy or who were operated urgently were excluded from the study.

Hemogram, biochemical parameters and tumor markers; Carcinoembryonic antigen (CEA) of the patients that operated for rectal cancers were tested before neoadjuvant treatment. In addition, pre-neoadjuvant pelvic magnetic resonance imaging (MRI), abdominal and thoracic computed tomography (CT), and postoperative pathology reports were evaluated. All patients received adjuvant oncologic treatment in postoperative follow-up. Of 25 patients underwent routine follow, 8 had developed metastasis. Postoperative follow-up of patients was performed as follows: Abdominal and thorax CT every 6 months in the postoperative first year, followed by every year CT ;CEA examination 2 years every 3 months postoperatively and every year colonoscopy exeamination was performed.

Albumin, CRP, Platelet, Neutrophil, Lymphocyte, Monocyte values were obtained as the inflammatory markers in the blood count test of the patients before neoadjuvant treatment. Based on these values, other inflammatory markers neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) were calculated. Similarly, MLR was calculated by division of monocyte count by lymphocyte count.

Patients were divided into 2 groups. Patients with no metastasis were named as group 1. The patients with metastasis were named as group 2.

Statistical Analysis

Analyzes were performed using SPSS software (version 15.0). In descriptive statistics, mean ± standard deviation or median (minimum-maximum) values for numerical variables and number and percentage values for categorical variables are expressed. The normality hypothesis was examined by Shapiro-Wilks test. In case parametric test assumptions were provided, two-way analysis of variance (T test) was used for repeated measurements and Mann Whitney u test was used for group comparison when parametric test assumptions were not provided. The ability of the measurements to differentiate the relapse status was examined by area under the curve (AUC) in the ROC analysis. Significance level was considered as $p < 0.05$.

RESULTS

Fifty-seven patients diagnosed with rectal cancer in the BAIBU general surgery clinic between 2012 and 2016 were retrospectively investigated. In this study, 25 patients who underwent neoadjuvant chemoradiotherapy and underwent full postoperative follow-up were evaluated. Eight of these 25 patients had metastasis until June 2019 (Table 1).

Table 1. Patients with recurrence and /or metastasis

Patients	Metastasis	Time of metastasis (months)	TNM
P1	metastasis	46	T3N0
P2	metastasis	40	T3N0
P3	metastasis	23	T3N1
P4	metastasis	29	T2N2a
P5	metastasis	26	T4N0
P6	metastasis	20	T3N1
P7	metastasis	16	T3N0
P8	metastasis	13	T3N1

According to monocyte values; there was a significant difference in monocyte values between groups with and without metastasis. Monocyte values of group 1 patients(0.45±0.2) were significantly lower than monocyte values of group 2 patients(0.7±0.35) ($p = 0.048$). In the group 2; monocyte values were higher (Table 2).

According to MLR values; there was a significant difference in MLR values between groups with and without metastasis. MLR values of group 2 patients (0.41)(0.25-1.73) were significantly higher than MLR values of group 1 patients(0.26)(0.10-0.76)($p= 0.014$). MLR values were higher in the metastasis group (Table 2).

Table 2. MLR and Monocyte Sensitivity and Specificity Values

	Cutoff Value for Predicting Metastasis in Rectal Cancer	Sensitivity	Specifity	AUC
MLR	≥0.14	87	65	0.809
Monocyte	≥0.43	87	53	0.75

Table 3. Laboratory parameters of the patients before Neoadjuvant treatment

	AUC	%95 CI	p
Albumin	0.511	0.235 – 0.788	0.930
CRP	0.658	0.429 – 0.888	0.210
NEU	0.640	0.386 – 0.893	0.268
PLT	0.625	0.360 – 0.890	0.322
LENF	0.688	0.463 – 0.912	0.137
MONO	0.750	0.554 – 0.946	**0.048**
NLR	0.728	0.517 – 0.939	0.071
PLR	0.603	0.348 – 0.857	0.415
MLR	0.809	0.633 - 0.984	**0.014**
CEA	0.806	0.581 – 1.000	**0.025**

No statistically significant difference was found between the mean age of the groups with and without metastasis (p = 0.426).

No statistically significant difference was found in terms of albumin, RDW, neutrophil, platelet, lymphocyte, NLR and PLR values (Table 3).

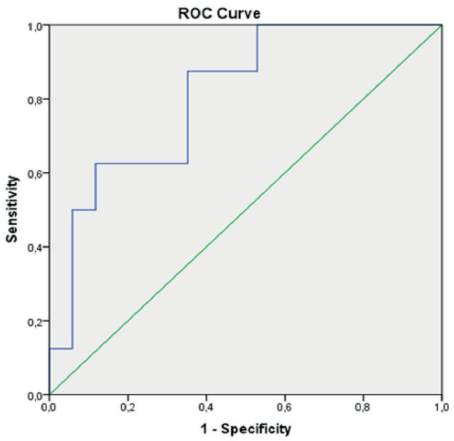

Figure 1. ROC curve for MLR

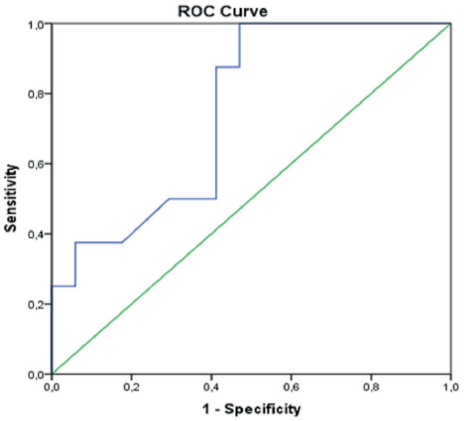

Figure 2. ROC curve for monocyte count

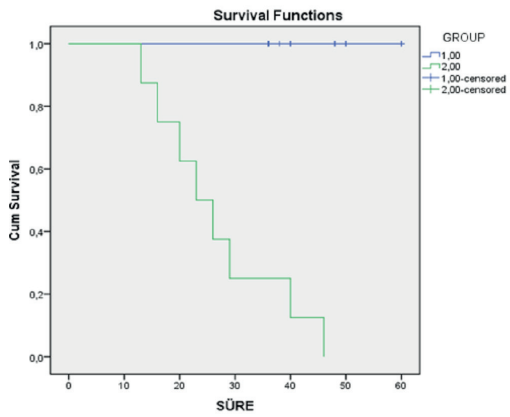

Figure 3. Kaplan-Meier Graphic of Rectum Cancer Patients According to Groups (group 1:non metastatic patients;group 2:metastatic patients)

Monocyte, MLR and CEA values showed significant performance in predicting metastasis in rectal cancer.

MLR showed the best performance in distinguishing metastasis (AUC = 0.809) (Figure 1). The performance of the monocyte marker to differentiate between metastasis status is moderate with AUC=0.75 (Figure 2).

ROC analysis, MLR value was found to be 87% sensitive and 65% specific for predicting metastasis in rectal cancer patients above 0.14 (Figure 1). As a result ROC analysis for monocyte value was found to be 87% sensitive and 53% specific for predicting metastasis in rectal cancer patients above 0.43 (Figure 2). Between group 1 and group 2 patients according to Kaplan Meier analysis , a significant difference was observed between survival times (Figure 3).

DISCUSSION

Rectal cancers are a health problem with a 5-year survival rate of 40-90% despite all the improvements in treatment possibilities (7). The development of metastasis limits disease-free survival despite all improvements in treatment modalities.

In this preliminary study, we investigated whether metastasis can be predicted by MLR values which are among the inflammatory indicators in blood tests in rectal cancer patients who underwent surgery after neoadjuvant chemoradiotherapy treatment.

The tumor microenvironment consists of extracellular matrix (ECM) and non-malignant stromal cells including fibroblasts, pericytes, immune cells and endothelial cells. Cancer-associated fibroblasts, pericytes, and innate immune cells, particularly tumor-associated macrophages are the main cell types that make up the tumor stroma.

Lymphocytes have an important role in immunity by initiating antitumor immune response (8,9). There are studies showing that MLR can be a good predictor of increased monocyte count since it is a marker of both the lymphopenia, an indicator of poor immune response, and the micro-environment of high tumor burden. In one study, they concluded that low lymphocyte monocyte rates are a negative prognostic marker in stage III colon cancer patients and that high-risk patients based on MLR may not benefit from adjuvant chemotherapy (10). Recently, it was found that preoperative lymphocyte and monocyte values, which reflect the degree of systemic inflammation, were correlated with prognosis in CRC patients (11,12).

As a result of the statistical analyzes, we found that monocyte values showed a significant difference between the groups with and without metastasis. Monocyte values were higher in the metastasis group. ROC analysis for monocytes showed a sensitivity of 87% and a specificity of 53% for predicting metastasis with a monocyte value of 0.43 and above. When the literature is examined, it is observed that monocytes and their derivatives in the micro-environment can produce factors that support the growth, migration, invasion and survival of tumor cells (13). However, another study showed that the number of tumor-related macrophages derived from circulating monocyte populations shows a good prognosis for CRC

patients (14). In another study, macrophages play a key role in the immune microenvironment of the tumor, promoting metastasis and tumor progression (15).

Increased monocyte and decreased lymphocyte counts in cancer patients may indicate decreased ability to stop tumor progression, indicating that LMR or MLR may be a good reflection of cancer progression (16). Similar to neutrophil-lymphocyte ratio, MLR is a much more effective prognostic marker in many solid tumors, predicting the inflammatory state (17). According to these information, our study showed that increased MLR value in rectal cancer patients with neoadjuvant CRT appeared to be a poor prognostic factor.

When studies on rectal cancer and inflammatory markers are examined, it is clear that non-invasive peripheral blood analysis can clearly help in assessing immune status in the tumor microenvironment. The relationship between systemic inflammation and poor prognosis of cancers can be explained by its effects on the immuno-microenvironment of the tumor. As a result of a study on colorectal cancer patients, it shows that rectal cancer patients with increased MLR values before treatment may have a better prognosis and longer survival than patients with low values (18). Another study suggested that low preoperative lymphocyte monocyte ratio in CRC patients was confirmed to correlate with worse survival and could provide information about prognosis by treatment decision in patients with CRC (19). The fact that CRC had less monocytes or a higher lymphocyte monocyte ratio in the blood concluded that there were more CD3 T cells in the nucleus of the tumor. This study showed that the concentration of immune cells in cancer tissue was closely related to inflammation, and more CD3 + T cells, less monocytes and higher lymphocyte monocytes ratio were found in the tumor (20). In this context, we concluded that metastasis in rectal cancer may be associated with higher MLR values.

In present study, we investigated the role of MLR in the blood before neoadjuvant therapy in predicting metastasis in patients treated with rectal cancer. Since the effects of monocyte and lymphocyte on the tumor microenvironment are known, the ratio of monocyte value to lymphocyte value was significant in our study. MLR values were found to be high in the metastasis group. According to ROC analysis, if MLR value is over 0.14, it is 87% sensitive and 65% specific in predicting the metastasis.

Our study is a preliminary study and small study population is the most important limiting factor.

CONCLUSION

The results of present study suggest that MLR value exceeding 0.14 in patients with rectum cancer before neoadjuvant therapy predicts the risk of metastasis. MLR values were found to be lower in patients with rectal cancer without metastasis. However, MLR values were significantly higher in patients with rectum cancer with metastasis. Therefore, we think that evaluation of preoperative MLR values in rectal cancer patients would be beneficial for clinicians about prognosis of the disease.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Statement of Ethics:This clinical research approved by Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee in 28/12/2018 with 414 number.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:359-86.
2. Lasry A, Zinger A, Ben-Neriah Y. Inflammatory networks underlying colorectal cancer. Nat Immunol 2016;17:230-40.
3. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature 2008;454:436-44.
4. Mytar B, Baj-Krzyworzeka M, Majka M, et al. Human monocytes both enhance and inhibit the growth of human pancreatic cancer in SCID mice. Anticancer Res 2008;28:187-92.
5. Mohri Y, Tanaka K, Ohi M, et al. Identification of prognostic factors and surgical indications for metastatic gastric cancer. BMC Cancer 2014;14:409.
6. Panni RZ, Lopez-Aguiar AG, Liu J, et al. Association of preoperative monocyte-to-lymphocyte and neutrophil-to-lymphocyte ratio with recurrence-free and overall survival after resection of pancreatic neuroendocrine tumors (US-NETSG). J Surg Oncol 2019;120:632-8.
7. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. J Natl Cancer Inst 2004;96:1420-5.
8. Kitayama J, Yasuda K, Kawai K, et al. Circulating lymphocyte is an important determinant of the effectiveness of preoperative radiotherapy in advanced rectal cancer. BMC Cancer 2011;11:64.
9. Ceze N, Thibault G, Goujon G, et al. Pre-treatment lymphopenia as a prognostic biomarker in colorectal cancer patients receiving chemotherapy. Cancer Chemother Pharmacol 2011;68:1305-13.
10. Stotz M, Pichler M, Absenger G, et al. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer. 2014;110:435-40.
11. Shibutani M, Maeda K, Nagahara H, et al. Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer. World J Gastroenterol: WJG 2015;21:9966.
12. Chan J, Diakos CI, Chan D, et al. Change in inflammatory status as a prognostic marker of overall survival in colorectal patients undergoing resection. J Clin Oncol 2016;34:6571.
13. Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006;124:263-6.

14. Chan JC, Chan DL, Diakos CI, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg 2017;265:539-46.
15. Galdiero MR, Bonavita E, Barajon I, et al. Tumor associated macrophages and neutrophils in cancer. Immunobiology 2013;218:1402-10.
16. Cao Y, Ni X, Wang Y, et al. Clinical and prognostic significance of combined plasma fibrinogen concentrations and the monocyte-to-lymphocyte ratio in patients with ovarian cancer. Ann Transl Med 2019;7:242.
17. Xiang J, Zhou L, Li X, et al. Preoperative monocyte-to-lymphocyte ratio in peripheral blood predicts stages, metastasis, and histological grades in patients with ovarian cancer. Transl Oncol 2017;10:33-9.
18. Ward WH, Goel N, Ruth KJ, et al. Predictive value of leukocyte-and platelet-derived ratios in rectal adenocarcinoma. J Surg Res 2018;232:275-82.
19. Song W, Wang K, Zhang R-j, et al. Prognostic value of the lymphocyte monocyte ratio in patients with colorectal cancer: A meta-analysis. Medicine(Baltimore). 2016;95:5540.
20. Guo G, Wang Y, Zhou Y, et al. Immune cell concentrations among the primary tumor microenvironment in colorectal cancer patients predicted by clinicopathologic characteristics and blood indexes. J Immunotherapy Cancer 2019;7:179.